



Alberta Heritage Foundation
for Medical Research

Sclerotherapy for leg varicose veins

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Comments relative to the information in this paper are welcome and should be sent to:

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ABBREVIATIONS/GLOSSARY

Abbreviations:

- AP - ambulatory phlebectomy
AVP - ambulatory venous pressure
Ccl I - compression stockings class I (<25 mm Hg)
Ccl II - compression stockings class II (25-35 mm Hg)
CEAP - Clinical signs, Etiology, Anatomic distribution, and Pathophysiology
cm - centimetre(s)
DSS - Double Syringe System
DVI - deep venous insufficiency
DVT - deep venous thrombosis
ES - endovascular sclerotherapy
Gp - group(s)
GSV - great saphenous vein (also called internal or long saphenous vein)
HS - hypertonic saline
HSD - hypertonic saline dextrose
Hz - Hertz
FDA - Food and Drug Administration in the United States of America
LAV - lateral accessory veins
mL - millilitre(s)
min - minute(s)
mo- month(s)
NSS- no (not) statistically significant
POL - polidocanol
RT - refill time
sec- second
SA - stab avulsion
SD - standard deviation



SFJ - saphenofemoral junction

SPJ - saphenopopliteal junction

SSV - small saphenous vein (also called external or short saphenous vein)

STS or STD - sodium tetradecyl sulphate

US - ultrasound/ultrasonography

USGS - ultrasound-guided sclerotherapy or echosclerotherapy

y - year(s)

Glossary:

Sources:

Dorland's dictionary and Mosby's dictionary ¹

Blood vessels - any one of the network of muscular tubes that carry blood (including arteries, arterioles, capillaries, veins, and venules)

Ecchymosis - a small hemorrhagic spot, a blue purplish patch (giving the appearance of a bruise)

Ligation - a surgical intervention that involves tying off a vein close to the site of incompetence to prevent blood flowing from the deep to the superficial system ¹;

Phlebectomy - the surgical removal (excision) of a vein or of a part of a vein

Sclerosis - an induration, or hardening; especially hardening of a part from inflammation, from increased formation of connecting tissue and in diseases of the interstitial substance; the term is used to designate hardening of the blood vessels

Sclerotherapy - the injection of sclerosing solutions in the treatment of hemorrhoids, varicose veins, or esophageal varices

Stab avulsion - an intervention used to treat multiple varicosities after saphenofemoral or saphenopopliteal ligation or in patients with perforator incompetence ¹; small incisions are made in the skin overlying each varicosity and the affected vein interrupted or excised

Stripping - a surgical intervention during which a wire, plastic, or metal rod is passed thorough the lumen of the saphenous vein and is used to strip the entire vein out of the leg ¹; this disconnects any superficial veins from the deep venous system;

Thrombosis - the formation, development, or presence of a thrombus

Thrombus - an aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation



Telangiectasia/telangiectasis - permanent dilation of groups of preexisting blood vessels (capillaries, arterioles, venules), creating small focal red lesions, which may present as a coarse or fine red line or as a punctum with radiating limbs (spider), usually in the skin or mucous membranes

Urticaria - a vascular reaction, usually transient, involving the upper dermis, representing localized edema caused by dilatation and increased permeability of the capillaries

Varicose - of the nature of or pertaining to a varix; unnaturally and permanently distended (said of a vein)

Varicosity - a varicose condition (abnormal condition usually of a vein, characterized by swelling and tortuosity); a varix or varicose vein

Varix - an enlarged and tortuous vein, artery or lymphatic vessels

Varicose vein - a tortuous, abnormally dilated vein (caused by defects of the valves or walls or both)

Vein/vena - vessel through which blood passes from various organs or parts back to the heart

Venule - any of the small vessels that collect blood from the capillary plexuses and join to form veins



EXECUTIVE SUMMARY

Objective

The Health Technology Assessment Unit of the Alberta Heritage Foundation for Medical Research was approached by the Alberta Health and Wellness to conduct a systematic review of the published research on the use of sclerotherapy to manage varicose veins of the legs.

Background

Leg varicose veins are tortuous, abnormally dilated vessels under the skin of the legs. Very small ones (<2mm in diameter) are referred to as telangiectasia, thread veins, or spider veins. Larger ones (>2mm in diameter) include varicosities of reticular veins and varicosities of saphenous veins or of their larger tributaries.

Although varicose veins are common, there is no consensus regarding their definition, or the best way to diagnose and treat them. Symptom relief is one of the main reasons for treatment. However, there are no universally accepted criteria for differentiating between symptomatic and asymptomatic varicose veins or for determining when treatment is medically necessary as opposed to cosmetic. Telangiectasia and reticular varicosities are commonly considered cosmetic problems that do not usually cause complications.

Sclerotherapy has been used as an alternative or an adjunct to surgery for treating varicose veins since the 1960s. It aims to prevent complications related to varicose veins, relieve symptoms, and improve leg appearance. The procedure involves directly injecting a chemical irritant (sclerosant) into the veins with a small needle. The sclerosant causes inflammation, thrombosis, and subsequent fibrosis of the vein.

The therapeutic outcome and safety of sclerotherapy depend on careful pre-treatment evaluation of each patient and on the provider's level of training and expertise. It requires many injections and can result in complications such as systemic allergic reaction to the sclerosant, post-treatment ulceration, and scarring. Recently, new approaches such as ultrasound-guided sclerotherapy, foam sclerotherapy and endosclerotherapy have been proposed to improve the safety and efficacy of standard sclerotherapy (with no ultrasound guidance).

Methodology

A systematic literature search (1998 to February 2004) was performed. The search included the Cochrane Library, CRD Databases, EBM Reviews - ACP, CINAHL, ECRI, MEDLINE, PreMEDLINE, EMBASE, and HealthSTAR. The web sites of practice



guidelines, regulatory agencies, evidence-based resources and other HTA agencies were also searched.

Randomized controlled trials (RCTs) comparing sclerotherapy with another treatment used for leg varicose veins or no treatment were included. A quality assessment of the selected RCTs was performed by one reviewer. Systematic reviews, guidelines and consensus documents on the use of sclerotherapy for this indication were also included. Extensive clinical input was obtained from a Canadian specialist with expertise in using sclerotherapy for leg varicose veins.

Results

The reviewed evidence suggests that:

- standard sclerotherapy appears to be efficacious in the management of reticular varicosities and telangiectasia; polidocanol, sodium tetradecyl sulfate, and hypertonic saline are potentially safe and effective sclerosants in the short-term, but there is no standard protocol for their use;
- the place of sclerotherapy as the first line of treatment for large varicose veins (saphenous or non-saphenous) remains controversial; and
- following surgery, sclerotherapy may achieve good results for varicose veins that have not fully disappeared or recur.

Endosclerotherapy and foam sclerotherapy (with ultrasound guidance) appear to be efficacious for uncomplicated varicose veins. However, these techniques are still evolving and need further evaluation.

Conclusions

The role of sclerotherapy in the management of leg varicose veins, particularly in relation to other treatment options, has yet to be clearly defined. The present review confirms the findings of previously published ones that there is no strong evidence to support or not support the use of sclerotherapy for symptomatic varicose veins. The questions on what sclerotherapy approach is most efficacious and for what group of patients are yet to be answered.

The public should be educated about using sclerotherapy for leg varicose veins. Potential serious complications and cosmetic deterioration must be weighted against the benefits of sclerotherapy.

The priority areas for future research are to establish uniform and objective criteria for diagnosis and patient selection; definitions for treatment failure and recurrence; and outcome measures. In addition, an objective evaluation of the efficacy and appropriate use of the numerous sclerotherapy techniques is essential.



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INTRODUCTION

This information paper addresses a request for information from Alberta Health and Wellness. The objective was to summarize and describe the current published evidence on the efficacy/effectiveness and safety of various types of sclerotherapy used to manage varicose veins of the legs. This document used the full text of the Technote prepared for the Alberta Health and Wellness (Corabian P, Harstall C). *Sclerotherapy for varicose veins of the legs*. Health Technology Assessment. Edmonton, AB: Alberta Heritage Foundation for Medical Research; October 2003. Report No. TN 40).

Sclerotherapy has been used since the 1940s as a non-surgical treatment for all types of varicose veins of the legs. Recently, new methods (such as ultrasound-guided sclerotherapy, and foam sclerotherapy) have been proposed to improve the safety and efficacy of traditional sclerotherapy. These techniques are mostly provided in highly specialized practice settings. Evidence about these techniques is still limited and claims about their benefits are regarded with some scepticism.

SCOPE

The intent of this paper was to answer the following questions (see Appendix A for more details on the methodology used):

- Is sclerotherapy effective for varicose veins of the legs and if so, is one approach more effective and for which group of patients (symptomatic, asymptomatic)?
- Are there standards to determine when the treatment for varicose veins is considered medically necessary and when it is considered to be cosmetic?
- Are there other approaches or variations of sclerotherapy emerging as treatment options for varicose veins of the legs?

To answer these questions, the methodological approach for this study included a review of the primary and secondary research studies (published since 1998 to present) reporting on (Appendix A):

Population – all types of varicose veins of the legs: primary and secondary; symptomatic and asymptomatic; very small, small and large (saphenous and non-saphenous).

Intervention – all sclerotherapy techniques (with or without ultrasound guidance; using liquid or foam sclerosing agents).

Comparator – conservative measures (such as compression therapy), other non-surgical options (such as laser therapy), surgical procedures, no treatment.

Outcome –symptom relief; vein recurrence; complication rate; cosmetic appearance.



Extensive clinical input provided by a Canadian phlebologist, with interest and expertise in the use of sclerotherapy for varicose veins of the legs, supplemented the review of the literature. The Canadian expert provided detailed answers to questions regarding the current status of sclerotherapy in Canada (*Expert review*).

This paper does not cover the use of sclerotherapy (alone or in conjunction with surgical interventions) for leg ulcer (venous ulceration) or other complications that may be caused by varicose veins.

BACKGROUND

The term "varicose veins" is used to describe dilated blood vessels under the skin of the legs, which have become visible, unsightly, abnormally enlarged or elongated, and/or knotted, tortuous, pouched, thickened or twisted ^{2, 3-15}. For the purpose of this review the term "varicose veins" is used as an umbrella term to encompass all types of leg varicosities.

These vessels can range from minor dilatations to large structures in the calf ^{2, 3, 5-15}. Small varicose veins include varicosities referred to as venulectasia, telangiectasia (also known as thread veins, spider veins, matted veins or dermal flares) and varicosities of reticular veins (also known as feeder veins). Large varicose veins represent varicosities of the saphenous veins and/or varicosities of their larger tributaries (see Figure 1). Large saphenous varicose veins include varicosities where an insufficiency of the saphenous trunk has been demonstrated. Large non-saphenous varicose veins include all varices where an insufficiency of the saphenous trunk has been excluded (i.e. perforators or perforating veins, tributaries, branches, local varicose veins, residual varicose veins, recurrent varicose veins).

There is no consensus regarding definitions, optimal diagnostic procedures and treatment strategies for varicose veins (*Expert review, Document-reply #1*) ^{1,7}. Although numerous classifications have been proposed, there is still no universally recognized classification scheme for varicose veins ^{2, 3, 5, 6, 8-20}.

Varicose veins

Varicose veins of the leg encompass the most frequent physical signs of chronic venous insufficiency (CVI) and is one of the most prevalent conditions in the general population (*Expert review, Document-reply #1*) ^{2, 3, 5, 7, 9-11, 13, 14, 18-24}. It is believed that varicose veins are caused either by primary abnormalities of the venous wall and/or valve leaflets or



Figure 1
Source ²³

- a) femoral vein
- b) long saphenous vein
- c) saphenofemoral junction
- d) popliteal vein
- e) short saphenous vein
- f) saphenopopliteal junction
- g) perforating veins



secondary changes due to previous venous thrombosis. These causes can lead to reflux, obstruction or both. Consequently varicose veins tend to be both chronic and recurrent. Most varicose veins are manifestations of primary venous insufficiency.

The prevalence of varicose veins is estimated to be between 2% and 40% ^{2, 3, 5, 7, 8, 9-14, 16, 18-25}. Although prevalence and incidence of varicose veins increase with age in both genders, they appear to be more common in women than in men. Risk factors include genetic predisposition, hormonal changes and pregnancy, obesity, lifestyle, venous thrombosis, leg injury, and prolonged standing ^{3, 5, 6, 7, 18, 19, 21-24}.

Varicose veins can be asymptomatic, produce aesthetic damage and/or discomfort or be responsible for functional and/or objective signs and symptoms of CVI (*Expert review, Document-reply #1*) ^{2, 3, 6, 7, 8, 9-14, 16, 18-27}. Commonly reported symptoms include local discomfort (aching, pain, itchiness, and burning sensation), generalized lower leg symptoms (leg-tiredness, restless leg syndrome, heaviness, skin changes and swelling/edema) and cramps.

Differentiation between symptomatic and asymptomatic varicose veins remains a challenge. The symptoms are not clearly defined and not always related to the degree or size of the varicose veins (*Expert review, Document-reply #1*) ^{2, 4, 27}. There is evidence to suggest that the severity of discomfort produced by varicose veins is disproportionate to the amount of the pathologic change present (*Document-reply #1, Appendix D*).

Varicose veins slowly progress with enlargement and distal extension and, if untreated, may eventually lead to severe complications such as bleeding, thrombophlebitis, and leg ulcer (venous ulceration) (*Expert review, Document-reply #1*) (*Dunn, personal communication*) ^{2, 7, 8, 12, 16, 18, 21-24, 28}. Varicose veins (particularly small ones) do not usually cause severe complications even if they are present over very long periods of time (*Dunn, personal communication*) ^{8, 14, 15, 23, 24}. Some evidence suggests that about 50% of patients with significant superficial venous insufficiency if left untreated will eventually suffer from CVI with severe complications ²⁹. However, the exact incidence of significant symptoms or severe complications in these patients has not been clearly determined yet (*Soriano, personal communication*) ⁴.

Treatment

The actual cause of varicose veins of the legs remains unclear and there is no known cure ^{2, 7, 10, 14, 19-23, 30, 31}. Treatment is palliative and aims to relieve symptoms, prevent and/or manage potentially disabling complications, and improve cosmetic appearance.

Asymptomatic varicose veins may be considered for treatment to improve cosmetic appearance (*Dunn, personal communication*) ^{3, 4, 14, 19, 22, 23}. Treatment for telangiectasia and reticular varicosities is most commonly performed for cosmetic concerns and may not be considered medically necessary ^{3, 14, 15, 19, 20, 23, 24, 26, 30, 32-35}. Although most of the



patients may be symptomatic as well ^{3, 5, 19} these varicose veins are usually considered cosmetic problems that do not usually cause severe complications ^{8, 15, 23, 24, 30}.

Patients with symptomatic varicose veins seek treatment to relieve symptoms, prevent worsening of the condition and manage complications ^{14, 15, 23, 24, 26, 28, 29, 32, 33-36}.

Treatment is considered medically necessary for varicose veins associated with complications such as pain, swelling/edema, skin changes, bleeding, and leg ulcers.

The variations in size, flow, depth and type of varicose veins preclude the possibility of a single effective treatment modality, particularly when viewed from a long-term perspective ^{2, 6, 7, 10, 11, 13, 19-22, 36, 37}. Variables considered include the chronic and recurrent nature of the varicosities, the goal of the treatment, patient preference, treatment-associated complications and cost-effectiveness. Criteria for evaluating treatment success include patient satisfaction, and haemodynamic and aesthetic factors. There may be varicose veins recurrences even after adequate treatment. Life long control usually involves a series of treatments.

Currently, several treatment options are available depending upon the pathology and the severity of the condition ^{3, 5-7, 11, 13, 14, 20, 28, 37-39}. Conservative measures, such as leg elevation and use of compression therapy (bandages or stockings), are considered appropriate for small varicose veins with questionable symptoms or those with mild symptoms and no severe complications ^{3, 14-16, 22, 23, 27, 28, 33, 34, 40}. The role of compression therapy is not limited to treatment of small symptomatic varicose veins as its use is very important in the management of large complicated varicose veins too (*Soriano, personal communication*) ^{5, 27, 36, 38}.

When conservative measures fail and for more complicated cases, the main treatment options are sclerotherapy and/or superficial vein surgical procedures (such as ligation and stripping) (*Dunn, personal communication*) ^{28, 36}. Many patients are treated using a combination of surgery, sclerotherapy and compression therapy. Other procedures such as radiofrequency ablation and laser therapy are also used in many patients (*Dunn, personal communication*), (*Salvian, personal communication*) ^{3, 28, 36, 41}.

SCLEROTHERAPY

Sclerotherapy has been frequently used worldwide (alone or in combination with surgery) to treat all types and sizes of varicose veins, primary and/or secondary in nature ⁹. It is a palliative treatment and is unable to stop the formation of new varices ^{12, 20, 37}. Expert opinion suggests sclerotherapy "may postpone and perhaps even prevent the development of chronic venous insufficiency of venous disease" (*Expert review, Document-reply #2*) ⁷.

At present the scientific evidence on definitive indications for sclerotherapy is lacking (*Expert review, Document-reply #2 and #5*) ^{10, 12}. Currently, it is the most commonly used



procedure for improvement of leg appearance. It is also used for symptom relief and for prevention of complications related to varicose veins.

The guiding principles for successful sclerotherapy are irreversible endothelial injury to the desired vein and permanently eliminating all sources of superficial reflux without causing any adverse effects (*Expert review, Document-reply #2*) 6, 9, 10, 12, 13, 17, 19, 21, 42-44. The procedure involves direct injection of a corrosive substance (referred to as sclerosing agent or sclerosant) into the varicose veins with a small needle. The sclerosant is designed to irritate or dehydrate, change the surface tension or destroy the endothelial cells to produce a small thrombosis that eventually results in permanent fibrosis of the vein. After massaging the injection site to evenly distribute the sclerosant, compression therapy may be applied for a few days or as long as 8 weeks (*Expert review, Document-reply #2*) 3, 5, 6, 13, 17, 22, 40, 45.

Sclerotherapy requires multiple treatment sessions, at intervals of 4 to 12 weeks, depending on the patient's tolerability of the treatment, response to the treatment and the strength of the sclerosing solution (*Expert review, Document-reply #2 and #4*) 5, 29, 36, 20, 40, 46. It may take up to 6 months for veins to completely disappear. Patients require no hospitalization and remain mobile and active after sclerotherapy.

Patient selection

Patient evaluation and selection (based on a precise diagnosis of the varicose condition) are critical in determining the feasibility of using sclerotherapy 2, 3, 5, 7-10, 12-14, 20, 21, 24, 29. Pre-treatment evaluation includes careful clinical history and physical examination and, when indicated, appropriate diagnostic tests (such as laboratory evaluation, ultrasound examination, plethysmography and other vascular testing).

Absolute contraindications for sclerotherapy include: known allergy to the sclerosing agent, severe systemic disease, recent deep venous thrombosis, local or general infection, inability to walk and severe arterial disease (*Expert review, Document-reply #2*) 5, 12, 20, 29, 36. Sclerotherapy should be performed with caution in pregnant or breast feeding women, or in patients presenting with allergic diathesis, hypercoagulability, and recurrent deep venous thrombosis.

It has been suggested that sclerotherapy should not be used in patients who fear needles, previously failed sclerotherapy, and in those with very fine telangiectatic vessels 17, 47.

Sclerosing agents

Sclerosants can be classified into detergents, chemical irritants, and osmotic agents, (Table 2, Appendix B). These agents vary in terms of their mechanism of action, sclerosing power, concentration, the pain provoked on injection and the incidence of other adverse effects. Although a variety of sclerosants are currently available, the ideal



agent (which would be effective, cosmetically pleasing, without any complications and painless) is yet to be developed ^{3, 5, 9, 12, 13, 20, 21, 36, 48}.

There is no universal consensus regarding the use of a specific sclerosant, its concentration or dose and specific technique for which type of varicose veins. The choice of sclerosant appears to be based on: its approval by regulatory bodies such as the Food and Drug Administration (FDA) in the United States and Health Canada; its minimum concentration and complication profile; patient's allergy profile, pain tolerance and previous treatment response; the type, size and site of the veins to be injected; and the provider's personal knowledge and experience ^{3, 5, 6, 11, 13, 17, 20, 21, 49}. The concentration and injected volume of the sclerosing agent depend on the interval between injections and whether it is the first injection or a re-injection ^{6, 9, 10, 12, 13, 17, 19-21, 42}. The duration of direct contact the agent has with the walls of the veins appears to be more important than the volume or rate of injection ^{17, 31, 42, 43, 50, 51}.

Techniques

All sclerotherapy techniques used in clinical practice are derived from one of the three "historic" sclerotherapy techniques, known as French or Tournay's technique, Swiss or Sigg's technique, and Irish or Fegan's technique (*Expert review, Document-reply #4*) ^{5, 13}. These methods differ in the overall treatment plan and in the use and duration of compression therapy following sclerotherapy.

A recent advance in traditional sclerotherapy is ultrasound-guided sclerotherapy (USGS) or echosclerotherapy (*Expert review, Document-reply #4*), ^{13, 17, 31, 39, 44, 48, 50, 52}. During this technique, developed in North America, the intra-venous position of the needle is controlled by both ultrasound and clinical observation. USGS purportedly increases efficacy and safety by providing visualization of the injection, diffusion of the sclerosant and the venous spasm that follows injection, the immediate identification of a perivascular injection, unfavorable anatomical situations (such as incompetent saphenous junctions, trunks and deeply situated perforating veins), post-operative recurrences and control of the results (*Soriano, personal communication*), (*Expert review, Document-reply #4*) ^{11, 19, 37, 53}.

Despite the reduced likelihood of intra-arterial injection of the sclerosant with USGS, intra-arterial injections have been reported (*Expert review, Document-reply #4*) ^{11, 19, 37, 53}. This has led to further modifications of the technique (endovascular sclerotherapy and transcatheter USGS) by the introduction of a catheter at the site of puncture (also called the "Canadian" method). These approaches have been used for greater saphenous vein or for perforator veins. Recently, the American Academy of Dermatology ¹² suggested that Duplex USGS may be used for the treatment of perforating veins because of the likelihood of perforating arteries and nerves running adjacent to the perforating veins.



Other modifications include Doppler-Guided Injection and Intravascular Ultrasound-Controlled Injection (IVUS) (*Expert review, Document-reply #4*). The hand-held Doppler-Guided Injection is used for those varices that are difficult to visualize. This approach is subject to accidental errors. IVUS involves sclerotherapy injections through an intravascular ultrasound probe. It provides possibility for evaluating vessel walls before, during, and after therapeutic interventions.

Foam sclerotherapy represents another advance in traditional sclerotherapy (*Expert review, Document-reply #4*) 13, 18, 29, 31, 44, 54-56. Sclerosant solutions have been transformed into special foams for traditional sclerotherapy (without ultrasound guidance) of minor varicosities and for USGS to treat saphenous incompetence and recurrent varicose veins. Different methods have been developed to create stable sclerosing foam and each method has its own advantages and disadvantages. Recently developed sclerosing foams are believed to be stronger than sclerosant solutions and to act longer at the vein site.

The wide range of different practices in sclerotherapy suggests a lack of uniformity in performing this treatment 3, 7, 9, 12, 13, 17, 20, 21, 42. Injection techniques vary in terms of patient position and the type, quantity, volume and concentration of the agent used (*Expert review, Document-reply #4*) 3, 10, 7, 9, 12, 20, 42. Other variations include rate of injection, time between injections and duration of post-treatment compression therapy (which can be immediate or not, local or on the whole leg, and also vary in terms of type of material, and/or pressure/class).

The technique used, the type of sclerosant, provider's training and experience, definition of recurrence and ultrasound factors (such as ultrasonography experience and the resolution of the system used) have been identified as potential aspects that may influence the therapeutic outcome (*Expert review, Document-reply #2 and #5*) 3, 7, 10, 13, 17, 20, 43, 44, 46, 48. Also, "the smaller the vein the more effective sclerotherapy" may be (*Dunn, personal communication*) 3, 7, 9, 10, 12, 13, 20, 21, 42.

Provider qualifications

Since "sclerotherapy can generate adverse reactions", it "needs to be performed judiciously by a trained professional in a controlled and safe environment" (*Expert review, Document-reply #2*). To be qualified, the provider is required to have training in an appropriate specialty, knowledge of the anatomy and physiology of the venous system, a good understanding of the etiology of varicose veins, appropriate training in the evaluation and experience in the treatment of CVI and its manifestations, and knowledge of the sclerotherapy mechanism of action 3, 7, 10, 12, 13, 17, 19, 20, 38, 43, 44, 46.

Sclerotherapy is performed by dermatologists, family practitioners, internists, gynecologists, and general, vascular, and plastic surgeons (*Expert review, Document-reply #5*) 12, 20, 28. Sclerotherapy for spider veins is also carried out by specialist nurses under



the supervision of experienced vascular surgeons¹⁸. Performance of USGS requires appropriate skills in both sclerotherapy and ultrasound and adds interventional radiologists to the list of people who now treat venous disorders^{17, 19, 29, 52}.

Side effects and complications

Sclerotherapy for varicose veins of the legs has been associated with various adverse events including^{3, 5-7, 9, 12-14, 17, 20, 21, 41, 44, 51, 57-59}:

- pain with injection, itching, cramps;
- slight or severe cutaneous pigmentation or hyperpigmentation (rates reported between 10% and 80%; temporary pigmentation (6-24 months) reported in about 10-30% of cases and permanent pigmentation in 5-7% of patients⁵⁸;
- localized urticaria;
- secondary telangiectasia or matting (rates vary between 5% and 75%);
- chemically induced phlebitis or periphlebitis;
- cutaneous necrosis or ulceration resulting in scar formation; and
- blurry and temporary loss of vision (sodium tetradecyl sulfate and chromated glycerine).

Patients should be informed about the possible side effects and complications^{6, 9, 10, 12, 13, 14, 17, 20, 21, 41, 42, 44, 55, 59, 60}. The occurrence of simple complications such as matting (neovascularization) and pigmentation is less acceptable when sclerotherapy is performed for cosmetic purposes rather than for functional venous disorders. The stronger the sclerosing agent and the higher its concentration the more likely the complications are to occur⁵.

Major complications are very rare but include accidental intra-arterial injection, deep venous thrombosis, superficial thrombophlebitis, pulmonary embolism, and systemic allergic reaction (anaphylactic shock) (*Expert review, Document-reply #2*)^{3, 5, 29}. Several accidental intra-arterial injections resulting in leg amputation have been reported (*Expert review, Document-reply #2*).

Regulatory approval and coverage

The most commonly used sclerosing agents are sodium tetradecyl sulfate (STS), hypertonic saline (HS), hypertonic saline dextrose (HSD), polidocanol (POL), and chromated glycerine^{3, 6, 13, 17, 20, 21, 57}. STS is FDA approved and also licenced by Health Canada (see Appendix B, Table 2). POL is currently undergoing FDA review and requires special approval before use from Health Canada. HS and HSD are not approved as sclerosants by the FDA. *Sclerodex*® (HSD) is widely used in Canada and is licenced by Health Canada for local injection in sclerotherapy. Chromated glycerine (*Chromex*®) is widely used in Europe but is not available in North America.



Coverage in Canada

In Alberta, the physician service for the injection(s) of sclerosing agents into symptomatic veins is an insured service when deemed medically necessary⁶¹. If performed only for cosmetic reasons it is not covered by the Alberta Health Care Insurance Plan.

Compression sclerotherapy (which includes multiple injections, compression bandaging and one post injection visit utilizing principles of Fegan) and repeat compression sclerotherapy are insured by the Ontario Health Insurance Schedule of Benefits for Physician Services⁶². Physician assistant fees for these procedures are currently considered not medically necessary and are no longer insured in Ontario^{62,63}.

"Simple sclerotherapy (removal of varicose veins)" is uninsured in Nova Scotia and has been de-insured in the province of Quebec and in Manitoba (*Expert review, Document-reply #5*).

Coverage in the United States

In the United States, insurance coverage varies and is considered both on the basis of the agent and the technique^{33,64,65}. In general, sclerotherapy is considered medically necessary and is covered when performed for symptomatic varicose veins that have failed previous conservative treatment (such as compression therapy) of 1.5 to 6 months duration. Insurance plans do not cover treatment of telangiectasia or spider veins if the treatment is performed solely for cosmetic reasons.

Some insurance plans consider ultrasound or duplex-guided sclerotherapy techniques as investigational and reimbursement is not available when they are performed solely to guide the needle or introduce the sclerosant into the varicose veins^{32,33,34,35,65,66}. A coverage policy by the United States Health Administration Center of the Department of Veterans Affairs⁶⁷ approved USGS for use on the smaller and greater saphenous vein system when the medical record documents a justified need for ultrasound as an adjunct to sclerotherapy.

AVAILABLE EVIDENCE ON EFFICACY/EFFECTIVENESS AND SAFETY

The literature search revealed no randomized controlled trials (RCTs) that compared sclerotherapy (with or without ultrasound guidance) with conservative measures (such as compression therapy) or watchful waiting.

Five RCTs⁶⁸⁻⁷² conducted to evaluate the safety and efficacy/effectiveness of sclerotherapy for leg varicose veins were considered for this review. Two systematic reviews^{1,13} recently produced on the effects of treatments in patients with varicose veins were also included in this review. Details of reviewed RCTs and an assessment of these studies' methodological quality are provided in Table 3 and Table 4, Appendix C.



The following commentary summarizes the reviewed evidence, presented according to the level of evidence (RCT or systematic review), type of varicose veins treated, and treatment approach. Information on upcoming research on this topic is also provided.

Reviewed RCTs

A prospective RCT was recently conducted by Labas et al.⁶⁸ to compare short- and long-term findings of different techniques of compression sclerotherapy using detergent sclerosants in patients with CVI (no details provided). Over a period of 10 years (1991 - 2000) the investigators treated patients by Sigg's technique using liquid POL, by Fegan's technique using liquid STS, and by Fegan's technique using a combination of both sclerosants. No description of study population (in terms of age, gender, and distribution of known confounders) was provided in the published report of the RCT. The results were considered to be good in cases of the disappearance of varices and eczemas, reduction of edemas, healed ulcers and relief of symptoms such pain, fatigue, tiredness and night cramps.

Statistically, significant differences ($p < 0.05$) were found only for the disappearance of varices and reduction of pain in favour of Fegan's technique. STS caused more complications such as local necrosis, hyperpigmentation and telangiectasis and POL caused more hypertension and collapse. The investigators concluded that compression sclerotherapy "is effective when properly executed in any length of vein no matter how dilated it has become". The recurrences were attributed more to inadequate technique than to the shortcoming of the procedure.

McCoy et al.⁶⁹ compared the relative efficacy of liquid HS and liquid POL for primary idiopathic leg telangiectasia and reticular feeding veins (with no major saphenous or perforator incompetence). No graduated compression was used following treatment. HS was equally effective as POL in terms of clinical and photographic assessments of vessel disappearance. However, POL caused more staining and matting. Although patients found HS more painful at injection, patient satisfaction at follow-up was higher with HS compared to POL. The investigators concluded that both agents have equal efficacy in sclerosing telangiectasia and reticular feeding veins, but POL causes more adverse effects.

Hamel-Desnos et al.⁷² recently conducted a prospective, multicenter RCT to study the elimination of reflux, the rate of recanalization, and possible side effects of foam sclerotherapy compared with liquid sclerotherapy using 3% POL (identical volumes) in incompetent GSV. No information was provided on age, gender and distribution of known confounders in the study population. Sclerotherapy was performed under ultrasound guidance in all study patients. The sclerosing foam was prepared using the Double Syringe System (DSS) method.



Follow-up after 3 weeks showed 84% elimination of reflux in the GSV with DSS foam versus 40% with liquid sclerosant ($P < 0.01$). At 6 months, six recanalizations were found in the liquid group versus two in the foam group. After 1 year, no additional recanalization was observed with either foam or liquid. Side effects did not differ between groups. The investigators concluded that the efficacy of DSS sclerosing foam is a superior therapy for GSV when compared with sclerosing liquid. Longer-term studies are underway.

The efficacy of treating **superficial leg telangiectasia with STS sclerotherapy versus long-pulsed 1064 nm Nd:YAG laser irradiation** was studied by Lupton et al.⁷⁰ The results suggested that patients with leg telangiectases responded better to sclerotherapy than to laser irradiation. Earlier vessel clearing and higher improvement scores for sclerotherapy were noted at each follow-up visit (at 1 month after the 1st session, and at 1 month and 3 months after 2nd session). Patients treated with sclerotherapy had fewer treatment sessions than patients treated with laser irradiation. The incidence of adverse effects was minimal and equivocal in both treatment groups. The investigators concluded that "sclerotherapy continues to offer superior clinical effect in the majority of cases. Laser leg vein treatment appears to be most beneficial in patients with telangiectatic matting, needle phobia, or sclerosant allergy".

Belcaro et al.⁷¹ evaluated the efficacy and costs of using **endovascular sclerotherapy (ES) (with high resolution ultrasound) compared with surgery alone or combined surgery and compression sclerotherapy** in patients with **varicose veins and pure superficial venous incompetence**. All approaches were reported to be effective in controlling the progression of venous incompetence, but, on a long-term basis (at 10 years follow-up) surgery appeared to be the most effective method. This study suggested that combined surgery and compression sclerotherapy may be more effective than surgery alone, particularly for distal veins. The venous system was still incompetent in 16.1% of the limbs treated with combined surgery and sclerotherapy as compared to 36% of the limbs treated by surgery alone. There was an 18.8% failure rate in controlling SFJ incompetence and a 43.8% failure in obliteration of distal saphenous reflux following ES.

Both surgery and surgery combined with compression sclerotherapy were more expensive than ES. However, ES was also followed by compression sclerotherapy of residual veins after three months and it was not clear whether that was included in the ES cost. The investigators concluded that ES was an effective, cheaper treatment option, but surgery after ten years was superior.

A quality assessment of the reviewed RCTs

As shown in Appendix C, Table 4, none of the reviewed RCTs stated the randomization and allocation concealment methods used. Three RCTs^{68, 71, 72} did not blind patients, providers or assessors of outcome to the intervention being used. In two studies the



outcome assessor was blinded to treatment ^{69, 70}. None of the studies ^{68, 69, 72} comparing different sclerosants blinded both their patients and treating physicians to the therapy used. Follow-up rate of 80% or more was achieved in all trials (Table 3, Appendix C).

The reviewed RCTs did not consistently provide information on aspects of interest (Table 3 and Table 4, Appendix C):

- Only one of the reviewed studies provided description of power calculation ⁷².
- None of the reviewed studies adequately identified the source population for included patients.
- Patient's characteristics were not adequately described in all studies.
- Most studies did not describe the distribution of known confounders.
- Two studies ^{69, 70} included only females, one study ⁷¹ included a mix of male and female subjects (in various percentages). In the remaining studies ^{68, 72} the gender was not mentioned.
- Pre- and post-treatment evaluations were not clearly described in all studies.
- Follow-up parameters were either not well defined or not validated.
- In three of the reviewed studies it was unclear whether the outcome evaluation was performed by the treating physician (s) or by independent external observer(s) ⁷⁰⁻⁷².
- In two of the studies which included independent assessors, it was unclear who examined the adverse events ^{68, 70}.
- Two studies reported results over short time lines ^{69, 70}.

Methods used for pre- and/or post-treatment evaluations varied and instrumental evaluations were included in all studies. The RCT comparing sclerotherapy (with or without ultrasound guidance) to surgery ⁷¹ used ultrasound examinations (colour Duplex) and AVP measurements for pre- and post-evaluations. The RCT comparing standard sclerotherapy to laser irradiation ⁷⁰ used post-treatment photographic assessment. Most studies used clinical evaluation ^{68-70, 72}.

None of the reviewed studies clearly stated the facility where the trial took place. However, it appears that all were conducted in highly specialized settings and their reported results may not reflect the practice outside of these settings. None of the studies provide information on the sclerotherapy provider's training and expertise.

Systematic reviews

The Cochrane Review by Tisi and Beverly ¹⁶ aimed to determine whether sclerotherapy was effective in terms of symptomatic improvement, recurrence and cosmetic appearance, and acceptable complication rates. This review intended to include RCTs of injection sclerotherapy versus graduated compression stockings or 'observation', or comparisons of different sclerosants, doses and post-compression



bandaging techniques on patients (>15 years of age) referred to a surgical outpatient clinic or primary care practitioner's office that had symptomatic and/or cosmetic varicose veins. Children presenting with varicose veins of the leg and patients with venous ulcers were excluded. A comparison of surgery versus sclerotherapy was outside the scope of this review.

The reviewers found very limited evidence on which to assess the relative merits of sclerotherapy as a treatment for leg varicose veins. The methodological quality of most of the twelve included RCTs was considered questionable. The main problems appeared to be in the randomisation process and in blinding of the patient and/or observer to the treatment. Most RCTs dated back to the 1980s.

There were no RCTs comparing injection sclerotherapy with simple observation. Also no RCTs comparing sclerotherapy for thread veins with laser treatment were found. One RCT published in 1973 compared sclerotherapy (using 0.5 ml STD injection) to graduated compression stockings in pregnancy (in 101 patients with primary or recurrent varicose veins). The reported results showed that sclerotherapy was more effective in terms of symptomatic improvement and cosmetic appearance (RR 1.61 [95% CI 1.19-2.18]).

Results reported by the other reviewed RCTs indicated that the type of sclerosant, local pressure dressing, degree and length of compression have no significant effect on the outcomes. Comparisons of STS to alternative sclerosants indicted no significant benefit from using alternative sclerosants to STS. The addition of local anaesthetic to the sclerosant reduced the pain from injection. Comparison of two pressure dressings showed no difference in their effect on erythema or the success of the sclerotherapy. The degree and duration of compression (elastic) had no significant effect on recurrence rates, cosmetic appearance or symptom improvement. Short-term bandaging was found to be better tolerated than more prolonged bandaging.

The Cochrane Reviewers found that for symptomatic varicose veins, there was no objective evidence to support or not support the continued use of sclerotherapy. They concluded that the reviewed evidence supported the place of sclerotherapy in modern clinical practice, which was limited to the treatment of recurrent varicose veins following surgery and thread veins. However, they recommended consideration of their results in conjunction with findings from an ongoing Cochrane Review (by Michaels and Kendall) that will assess RCTs comparing surgery to sclerotherapy and help determine the overall place for sclerotherapy as a procedure for treating varicose veins.

Tisi recently produced a *Clinical Evidence* summary¹ on the effects of treatments such as surgery, compression stockings and injection sclerotherapy in adults with varicose veins. The review (using *Clinical Evidence* search and critical appraisal, July 2003) was focused on uncomplicated varicose veins and excluded treatments for chronic venous



ulceration or other complications. It also excluded studies that examined only treatments for thread veins or spider veins or superficial telangiectasia.

Based on the reviewed evidence of the use of injection sclerotherapy it was concluded that the effectiveness of using injection sclerotherapy for this indication was unknown¹. No RCTs comparing sclerotherapy versus compression stockings or versus no treatment were located. One short-term RCT (published in 2003) reported no statistically significant difference between POL and STS for improvement in the appearance of varicose, reticular and/or telangiectatic leg veins without incompetence at the saphenofemoral or saphenopopliteal junctions. A long-term large multicentre RCT (published in 2003) reported a similar incidence of new varicose veins at 5 or 10 years with standard sclerotherapy (low dose STS), high dose STS standard sclerotherapy, and foam sclerotherapy (using ultrasound guidance) in adults with uncomplicated primary varicose veins and incompetence of the long saphenous vein at the SFJ.

Based on the results reported by four of the reviewed RCTs (one published in 1972, one published in 1993, and two published in 2003) Tisi concluded that surgery was more effective than sclerotherapy in terms of reduced recurrence of varicose veins and incidence of new varicose veins at 1 and 10 years¹. Although the effects of surgery versus injection sclerotherapy therapy may vary according to the site of vein incompetence, none of the reviewed RCTs reported relative effects with regard to the sites of venous incompetence.

The *Clinical Evidence* summaries are based on a thorough search and appraisal of the literature, looking for good systematic reviews and, where these are lacking, individual randomised controlled trials (<http://www.clinicalevidence.com>). The summaries are written by clinicians with skills in epidemiology and are peer reviewed.

Upcoming Research

The National Coordinating Centre for Health Technology Assessment in the United Kingdom is currently undertaking a review that will assess the cost-effectiveness of the commonly used treatments for varicose veins by way of a Markov decision model⁷³. The data for the modelling will be obtained through a combination of systematic review and the collection of retrospective and prospective data on patients referred to hospital for treatment. This will include RCT data from a group of patients with uncomplicated varicose veins in whom conservative treatment, sclerotherapy and surgery will be compared⁷⁴. Patients with ulceration and recurrent veins will be excluded.

The model will allow an assessment of the incremental cost-effectiveness of each treatment modality in sub-groups of patients based upon their symptomatic, investigative and demographic features⁷³. Patient and societal priorities for treatment



will be assessed using a "willingness to pay" technique. This review is expected to be published in 2005.

CONSENSUS DOCUMENTS AND GUIDELINES

Given the lack of agreement on the various techniques, clinical indications and results of sclerotherapy for varicose veins of the legs, working groups and international consensus conferences were organized to develop consensus statements and guidelines^{2, 7, 10, 12, 38, 60}. These activities took into consideration the scientific literature available, the personal experiences of the participating experts and the results from an international questionnaire concerning the practice of sclerotherapy. Given the lack of of good scientific evidence on the topics discussed, recommendations were mostly based on professional agreement.

Table 1 provides a summary of the recommendations provided in the documents released as a result of these activities^{2, 7, 10, 12, 38}. These recommendations concern sclerotherapy for primary varicose veins of the legs.

Table 1: Recommendations from consensus reports and guidelines^{2, 7, 10, 12, 38}

Type of varicose veins	Recommendations
All stages of primary varicose veins	Surgery to relieve symptoms or prevent complications ²
Telangiectasia, reticular varicose veins, symptomatic without reflux	Sclerotherapy to relieve pain ⁷
Telangiectasia, reticular varicose veins with superficial venous reflux	Sclerotherapy for improvement in cosmetic appearance ⁷
Venulectasia, telangiectasia and small varicose veins (reticular varicose veins)	Sclerotherapy ^{10, 12, 38} No surgery ⁷
Non-saphenous varicose vein including residual and recurrent varicosities after surgery, local varicose and varicose tributaries to saphenous trunk without saphenous insufficiency	Sclerotherapy ⁷ Sclerotherapy ¹⁰ , choice between surgery or sclerotherapy based on physician's experience and vein characteristics
Large tributaries feeding varicose veins but without evidence of reflux in the large veins	Surgery ⁷ Sclerotherapy (side branch varicosity: veins that branch off a truncal varicose vein or mid and posterior thigh perforating vein) ¹² Duplex USGS (perforating veins) ¹² Sclerotherapy (with or without Duplex scanning guidance) for perforating veins ³⁸
Saphenous veins with reflux	Surgery ^{2, 7}



Table 1: Recommendations from consensus reports and guidelines (cont'd)

Type of varicose veins	Recommendations
Long saphenous varicose veins	Surgery ⁷ Sclerotherapy ³⁸ (after points of reflux adequately treated with sclerotherapy and/or ligation) No agreement on role of sclerotherapy ¹⁰ Sclerotherapy ¹²
Short saphenous veins	Surgery or sclerotherapy ^{7, 10, 38} (no evidence on whether surgery or sclerotherapy is best treatment ^{7, 10} ; surgery is treatment of choice for saphenous varicose veins ⁷ ; sclerotherapy after points of reflux adequately treated with sclerotherapy and/or ligation ³⁸)

EXPERT OPINION AND CLINICAL PRACTICE

According to the advice obtained from one Canadian specialist in phlebology who has expertise in the use of sclerotherapy for varicose veins (*Expert review*):

- Currently, there are no generally accepted criteria to determine when to treat varicose veins and how to differentiate a cosmetic varicose presentation from a medical varicose presentation.
- There are no sclerotherapy treatments that are specific for asymptomatic versus symptomatic varicose veins. Dosages and techniques of sclerotherapy can be specific to the type, size and anatomical location of varicose veins, but not to the symptoms they engender.
- The outcome and safety of sclerotherapy depend very much on the sclerotherapist's training and expertise and on careful pre-treatment evaluation of each patient.
- Sclerotherapy performed by trained hands is considered standard of care for primary varicose veins. However:
 - Sclerotherapy is the preferred treatment for small varicose veins and is most effective in relieving leg discomfort associated with telangiectasias.
 - Sclerotherapy may be indicated for large non-saphenous varicose veins (without reflux) but there is no agreement on its role in the management of perforators.
 - There is no consensus on the role of sclerotherapy in the management of GSV.
 - SSV can be treated by either sclerotherapy or surgery.
 - If considered for GVS or SSV, sclerotherapy should be performed only by experienced providers.



- For secondary varicose veins (i.e., varicose veins with reflux and/or obstruction of the deep venous system), sclerotherapy can be considered after careful functional assessment.
- Standard or compression sclerotherapy is standard of care for small varicose veins.
- USGS is the standard of care for large varicose veins in all groups of patients. It was always deemed as "a more efficient visualization method of performing an established procedure".
- Modifications of the USGS method are still in the experimental stage. The Transcatheter Duplex USGS has been repeated worldwide for over 10 years, and no intra-arterial injection has been reported.
- Foam sclerotherapy is a promising method but is still evolving and undergoing research.
- Endovenous Laser Ablation and Radiofrequency Venous Closure are emerging as promising treatments for varicose veins.

In the light of the inconclusive evidence regarding the role of sclerotherapy (with or without ultrasound guidance) as a medical or cosmetic treatment, several coverage options have been put forward (*Expert review, Document-reply #5*). In response to the outlined options, it has been suggested that deinsuring sclerotherapy will lead to significant morbidity in many patients, will increase work absenteeism, and will greatly affect the poorer segments of the population (*Hill, personal communication*), (*Moniuszko, personal communication*). Maintaining the current guidelines would be "the most reasonable course of action" until data from well designed and conducted RCTs become available (*Hill, personal communication*).

Clinical Practice

The literature search identified three questionnaire-based studies regarding the international practice of sclerotherapy^{57, 75, 76}. The results suggested a role for sclerotherapy as the first option for managing small varicose veins and as the treatment of choice for missed/residual varicose veins following surgery. Some results also showed that sclerotherapy (alone or in combination with surgery) was preferred to surgery alone for the treatment of tributary veins^{57, 75, 76}. Sclerotherapy was used and preferred less in countries where the respondents were vascular surgeons^{57, 75, 76}.

A wide range of practices in sclerotherapy are used worldwide and the technique used seems to depend on the country rather than on the basis of results obtained from clinical trials⁷⁶. Standards of care for practicing sclerotherapy are yet to be set and there is a need for formal education and systematic training in providing this procedure (*Soriano, personal communication*), (*Moniuszko, personal communication*)⁵⁷. Traditionally, in North America the teaching in this area has been conducted in the form of tutorials,



preceptorships and teaching courses by Phlebology societies, since universities do not teach courses in phlebology.

In Canada, sclerotherapy has been provided by many specialists in angiology⁷⁶. However, across the country the perception of sclerotherapy is mixed (*Expert review, Document-reply #4*). In the Province of Quebec sclerotherapy is accepted by the medical community as it is in Europe. In the other provinces and territories, the medical community's perception of sclerotherapy is similar to that in the United States where currently most physicians do not understand the indications, safety and efficacy of sclerotherapy.

In Alberta, the College of Physicians and Surgeons does not certify providers of sclerotherapy or specifically regulate the practice of this procedure (*College of Physicians and Surgeons of Alberta, personal communication*). An exception is endovenous laser sclerotherapy, which is restricted to accredited facilities because of its invasiveness and technical nature.

DISCUSSION

Sclerotherapy is a procedure that has evolved during the last four decades. It has been proposed as a non-surgical treatment option and has been frequently used (alone or in combination with surgery) for all types of varicose veins. However, the exact role of sclerotherapy in the management of varicose veins remains to be addressed.

Based on results from most recent research, the present review confirms the findings obtained by previously published systematic reviews^{1, 16} that there is no strong evidence to support or not support the use of sclerotherapy for symptomatic varicose veins. The role of sclerotherapy may be more clearly defined by upcoming research.

The questions on what sclerotherapy approach is most efficacious and for what group of patients with varicose veins are yet to be answered. Two of the reviewed RCTs^{68, 69} attempted to answer the question on which approach and which sclerosant is more effective for standard sclerotherapy of primary varicose veins. However, their results are not comparable as their investigators took different approaches. These studies included different populations, used different protocols and evaluated treatment response using different approaches.

The role of sclerotherapy in relation to other treatment options for varicose veins has not been clearly defined. One RCT comparing standard sclerotherapy to laser irradiation⁷⁰ indicated that standard sclerotherapy offers superior short-term clinical effect in the majority of patients with leg tangiectasia. Laser therapy may be an alternative in some patients for whom sclerotherapy is not recommended. However, laser therapy has been developed recently and its place as a reference treatment for any type of varicose veins has yet to be determined.



Over the long term the results of standard sclerotherapy have been mediocre to poor when compared to surgery or combined surgery and sclerotherapy in terms of recurrence rate and occurrence of new veins ^{1,71}.

Evidence about the new sclerotherapy approaches using ultrasound guidance (such as endovascular sclerotherapy and foam sclerotherapy) for treating patients with saphenous varicose veins is still limited ^{1,71,77}. The new methods may well offer some advantages for certain patients, but they need further evaluation. Endovascular sclerotherapy was found to be cheaper than surgery but not as effective as surgery in the long-term ⁷¹. There was no comparison with standard sclerotherapy, only with combined surgery and standard sclerotherapy.

Echosclerotherapy or USGS for varicose veins gained further importance in combination with sclerosing foam ^{54,72}. One recent prospective multicentre RCT ⁷² reported that USGS is more effective in terms of elimination of reflux in incompetent GSV at 3 weeks when DSS foam is used versus sclerosing liquid. Data from one of the RCTs reviewed by Tisi ¹ indicated that using the Irving technique of ultrasound-guided foam sclerotherapy might obtain, in selected subjects with uncomplicated primary varicose veins, results comparable to surgery at 10 years follow-up. However, this foam sclerotherapy technique still needs refinements ⁷⁷.

Although a wide variety of approaches to sclerotherapy are currently used, the appropriate techniques and agents to be used for various types of varicose veins are still debated ^{10,57}. There is a need for uniformity and objectivity for diagnosis, definition of patient selection criteria, definition of treatment failure, appropriate outcome measurement and definition of vein recurrence ⁷⁶. Further research is needed to better understand the pathogenesis of varicose veins ⁴.

In clinical practice it appears that the use of sclerotherapy is limited to treatment of small varicose veins (including telangiectasia and reticular veins), residual veins after surgery and small tributary veins without reflux (Hill, *personal communication*) ^{5,7,8,16,17,28,29,37,38,57,60,75,76}. Vascular surgeons use sclerotherapy mostly to treat small varicose veins and residual varicose veins following surgery ^{57,75,76}. Many of the other medical specialists and generalists practising sclerotherapy may choose to use it (alone or in combination with surgery) also for tributary veins (Hill, *personal communication*) ²⁹.

According to the reviewed literature, well-performed sclerotherapy (by appropriately trained and experienced hands, using appropriate techniques and injecting appropriate agents) may have desirable results in many patients. Currently sclerotherapy is provided by many specialists. However, there are no accurate methods to evaluate the provider's training and skills (*Expert review, Document-reply #5*) ^{3,7,10,13,17,20,43,44,46}. Also, there is a need for systematic training in sclerotherapy and definitive standards of care for practicing this procedure. In Alberta, the College of Physicians and Surgeons



does not certify providers of sclerotherapy or specifically regulate the practice of this procedure.

In Canada many physicians currently choose sclerotherapy or combined surgery and sclerotherapy over surgery alone for treating various types of varicose veins. *Sclerodex*® (HSD) is widely used and is licenced for local injection in sclerotherapy. STS is also licensed by Health Canada, but POL requires special approval before use. Information gathered from various sources suggests that this intervention is covered in Alberta when deemed medically necessary and there is limited coverage for it in Ontario. It is uninsured in Nova Scotia and has been de-insured in Manitoba and in the Province of Quebec.

CONCLUSIONS

Treatment of varicose veins of the legs is a field that has many conflicting claims. Although varicose veins are a common finding in the general population, there is still no consensus regarding their definition, or the optimal diagnostic procedures and treatment strategies for these conditions. Symptom relief is one of the main reasons for which treatment of varicose veins is considered. However, the specific symptoms and criteria that differentiate between symptomatic and asymptomatic varicose veins are not clearly defined.

Consensus regarding generally accepted criteria to determine when treatment for varicose veins of the legs is medically required and when it is to be considered cosmetic, have yet to be reached. However, it appears that treatment for telangiectasia and reticular varicosities is most frequently considered for cosmetic purposes.

The reviewed primary research still does not allow a firm scientific judgement on the effectiveness of using sclerotherapy for varicose veins of the leg. The role of sclerotherapy, particularly in relation to other types of treatment for varicose veins, has yet to be clearly defined. The reviewed literature from 1998 onwards, although limited, reflects that, if used by an appropriately trained and experienced provider:

- Standard sclerotherapy (without ultrasound guidance) appears to be the treatment of choice in the management of reticular varicosities and telangiectasia (for relief of pain and/or discomfort and vessel disappearance in the short term). POL, STS and HS are potentially safe and effective agents for this indication. Laser irradiation may be an alternative to sclerotherapy for those patients who have allergies to sclerosants or have a phobia of needles.
- The place of sclerotherapy as the first line of treatment for large varicose veins (saphenous or non-saphenous) remains controversial.
- Sclerotherapy may achieve good results following surgery for residual varicose veins.



- Endovascular sclerotherapy and foam sclerotherapy (with ultrasound guidance) appear to be efficacious for uncomplicated primary varicose veins associated with saphenous incompetence in terms of recurrence rates and occurrence of new veins in the long-term. Although promising, these techniques are still evolving and need further evaluation.

Sclerotherapy requires multiple injections of a chemical irritant and is associated with the possibility of cosmetic deterioration and serious complications. Its outcome and safety depend on careful patient evaluation and selection and on the provider's training and expertise.

The public needs to be educated about the use of sclerotherapy for varicose veins and the possible adverse events associated with it. Potential for intra-arterial injections, thromboembolism and systemic allergic reactions to the injected sclerosant, and cosmetic deterioration must be weighted against the benefits of the treatment.

In North America, health insurance coverage for sclerotherapy (with or without ultrasound guidance) as a treatment for varicose veins varies. If the treatment is considered for cosmetic reasons only, it is generally not covered.

Since the scientific literature lacks definitive indications for sclerotherapy, further objective assessment of sclerotherapy is warranted to clearly define its place and assist in setting definitive standards of care. Appropriate, well-designed multicentre, long-term RCTs are needed to compare the various sclerotherapy approaches (with or without ultrasound guidance) to other treatment (surgical or non-surgical) options for specific types of varicose veins^{7,8}. Future RCTs should adopt detailed protocols, define subjective symptoms, provide objective findings, including instrumental investigations and use standardized treatments. Cost analysis should be included.



APPENDICES

APPENDIX A: METHODOLOGY

Search Strategy

A literature search of relevant databases for published articles on the safety and efficacy/effectiveness of using sclerotherapy in patients suffering from varicose veins of the legs was conducted in April 2003 and an update literature search was run in February 2004. The searches were limited to publication dates 1998 to date, where such function is available, English language and human studies.

Database	Platform	Searched	Search Terms [†]
Core Databases			
The Cochrane Library	Issue 1, 2003 Issue 1, 2004 Licensed Resource Update Software	April 2003 Feb 2004	sclerotherapy and varicose veins Limits: 1998 to 2004
CRD (UK): Health Technology Assessment Database NHS Economic Evaluation Database Database of Reviews of Effects	http://nhscrd.york.ac.uk	April 2003 Feb 2004	(varicose-veins or varicose veins or sclerotherapy) AND (leg or legs)
PubMed National Library of Medicine (MEDLINE, Pre- MEDLINE)	http://www.pubmed.gov	April 2, 2003 Feb 2, 2004	#1 sclerotherapy #2 varicose veins #3 leg OR legs #4 varicose veins/therapy #5 varicose veins/surgery #6 #1 AND (#2 OR #3) #7 #3 AND (#4 OR #5) #8 #6 OR #7 #9 #8 AND in process [sb] #10 #8 Limits: Publication date from 1998 to 2004, English, Meta-analysis, Human #11 #8 Limits: Publication date from 1998 to 2004, English, Practice guideline, Human #12 #8 Limits: Publication Date from 1998 to 2004, English, Randomized Controlled Trial, Human #13 #8 Limits: Publication Date from 1998 to 2004, English, Review, Human #14 #9 OR #10 OR #11 OR #12 OR #13



Database	Platform	Searched	Search Terms [†]
Core Databases			
ISI: Web of Science Science Citation Index and Social Sciences Citation Index	Licensed Resource ISI	April 2003 Feb 2004	varicose veins AND sclerotherapy (title search) Limits: 1998-2004, English language only
EMBASE	Ovid	1996- 2003 Week 13, 1988-2004 Week 5	#1 varicose veins.mp. or exp varicosis/ #2 exp sclerotherapy/ or exp endoscopic sclerotherapy/ or sclerotherapy.mp. #3 exp leg vein/ or exp leg blood flow/ or exp lower leg/ or exp leg/ or legs.mp. or exp leg varicosis/ #1 and #2 and #3
EBM Reviews – ACP Journal Club	Ovid	1991- Jul/Aug 2003	#1 varicose veins.mp. [mp=title, abstract, full text, keywords, caption text] #2 sclerotherapy.mp. #3 #1 and #2 Limit: year=1998-2004
MEDLINE & PreMEDLINE	Ovid	1966-2004 Jan Week 3	#1 varicose veins.mp. [mp=ti,ab,rw,sh] #2 sclerotherapy.mp. #3 (leg or legs).mp. #4 #1 and #2 and #3 Limits: English, Human, 1998-2004
HealthSTAR	Ovid	1987-Jan 2004	#1 exp sclerotherapy/ #2 exp varicose veins/ #3 #1 or #2 Limits: Human, English language, Non-Medline, 1998-2004

Notes: † is a truncation character that retrieves all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc. In databases accessed via the Ovid platform the truncation character is \$.

A broad Internet search was also conducted using the meta-search engine (Copernic Agent 6.0 (sclerotherapy, varicose veins). In addition, the following Internet sites were checked (in April 2003 and in February 2004):

- Alberta Medical Association (sclerotherapy)
- Blue Cross Blue Shield, Technology Evaluation Centre
- Cabot (Canadian Health Research Index) (varicose veins, sclerotherapy)
- ClinicalTrials.gov (varicose veins, sclerotherapy)
- CMA INFOBASE: Clinical Practice Guidelines (sclerotherapy or varicose veins)



- Institute for Clinical Systems Improvement (ICSI)
- NLM Gateway (varicose veins AND sclerotherapy)
- National Guideline Clearinghouse (sclerotherapy or varicose veins)
- National Institute for Clinical Excellence (NICE) (varicose)
- National Research Register (Issue 1, 2003) (sclerotherapy and varicose veins)
- STEER
- University Health System Consortium (UHC)
- U.S. Food & Drug Administration

The reference lists of all retrieved articles were examined for studies/papers that were missed by the electronic searches.

The review of the literature was supplemented with extensive clinical input from a Canadian specialist in phlebology with expertise in using sclerotherapy for treating varicose veins. A list of questions (see Appendix D) was sent to the expert, who conducted a literature review and provided detailed answers to each of the questions asked. The responses were received in five separate documents (*Document-reply #1 - #5*). These replies are presented in one grey literature document (*Expert review*), which is available upon request.

Also contacted were:

- Health Canada, Therapeutic Products Directorate for information on regulatory status of various sclerosing agents in Canada; and
- Dr. Jonathan Michaels, Clinical Director, Sheffield Vascular Institute in the United Kingdom, member of the Cochrane Peripheral Vascular Diseases Review Group for information on the current status of the Cochrane review of RCTs comparing surgery versus sclerotherapy for varicose veins.

Screening and Reviewing the Literature

The studies identified by the search strategy were retrieved, reviewed and assessed to determine the relevance of each study by one reviewer (PC). Their inclusion/exclusion was determined on the basis of a list of inclusion and exclusion criteria developed for this study.

Included were:

- published reports of RCTs conducted prospectively to determine the safety and efficacy of sclerotherapy when compared to other treatments used for varicose veins (such as compression therapy or surgery), or no treatment;
- published reports of RCTs conducted prospectively to compare different sclerosing agents, doses, or post-sclerotherapy compression techniques used for varicose veins;



- systematic reviews and critical appraisals reporting on the safety and efficacy/ effectiveness of sclerotherapy as a treatment for varicose veins (those which provided a description of their search strategy, review methodology and inclusion/exclusion criteria);
- guidelines, position papers, consensus statements or minimum standards for the use of sclerotherapy to treat varicose veins;
- guidelines, position papers, consensus statements on definition diagnosis or treatment of varicose veins;
- overview articles, commentaries and discussion papers presenting background information on varicose veins and on the use of sclerotherapy for this clinical problem.

Non-randomized controlled trials, cohort studies, case series, case reports, editorials, letters and technical reports were not included. Also excluded were studies evaluating treatments for leg ulcers (venous ulcerations), variceal bleeding or other complications that may be caused by varicose veins.

Although mostly articles published in English and after 1998 were selected, some papers (presenting relevant information on the topic) published in French and/or before 1998 were retrieved, translated by one reviewer (PC) and quoted when appropriate.

Details of the RCTs included for review and their results are summarized in tabular format (see Table 3, Appendix C). A quality assessment of these trials was performed by one reviewer (PC) as part of the data extraction process (see Table 4, Appendix C). The evidence itself was not graded but it was described as potential sources of bias that should be taken into account when interpreting the reported results.

The methodological quality of each of the reviewed RCTs was considered in terms of the information provided in their published reports on the randomization method, adequacy of allocation concealment, proportion of patients lost to follow-up, blinding of outcome assessment and sample size calculation. Also considered were the information provided on selection of study population (to identify the source population for patients and how they were recruited), inclusion/exclusion criteria and the selected patients' characteristics as well as details of the interventions used and pre- and post-treatment evaluations, and the reporting of outcomes in the published report.



APPENDIX B: SCLEROSING AGENTS

Table 2: Sclerosing agents (Document-reply #4, Appendix D) 3, 17, 20, 23, 42, 49, 78

Agent (brand names)	Description and Usage	Complication profile	Regulatory status
Hypertonic saline (HS) Brand names: None	- hyperosmotic agent; caustic sclerotic action; readily available; rapid action; weak sclerosing effect - commercially available in 20% or 23.4% concentrations - less effective for larger thicker-walled varicose veins; mostly used for telangiectatic veins	Pain (stinging and cramping) High risk of skin necrosis Highly ulcerogenic Hyperpigmentation Low allergenic risk	Not FDA approved as sclerosant; under FDA review
Sodium salicylate Brand names: Saliject®	- hyperosmotic agent; relatively weak sclerosing effect - can be used at 6% to 60% concentration - needs to be diluted to 6% and 30% concentrations for general use	Very painful upon injection Allergy is rare	Saliject® is licensed by Health Canada for local injection in sclerotherapy
Hypertonic saline dextrose (HSD) Brand names: Sclerodex®	- mild hyperosmotic agent (similar to HS); weak sclerosing effect - characterized by high viscosity; remains in treated veins - available in one concentration only - less effective for larger thicker-walled varicose veins	Pain and muscle cramps (less than with HS) Low allergenicity Low risk of skin necrosis	Not FDA approved as sclerosant; Sclerodex® is licensed by Health Canada for local injection in sclerotherapy



Table 2: Sclerosing agents (cont'd)

Agent (brand names)	Description and Usage	Complication profile	Regulatory status
Sodium tetradecyl sulfate (STS) Brand names: Fibrovein [®] , Sotradecol [®] , STD [®] , Tromboject [®] , Trombovar [®]	- detergent (emulsifier); colorless; expensive; - strong sclerosing effect; rapid dissolution of endothelium; effective at low concentrations - commercially available in 0.2% to 3% concentrations; - higher concentrations used for large veins (1.5%-3%) - can be diluted for use in telangiectatic and reticular veins	Pigmentation is not rare Necrosis of skin (with extravasation of concentrations >0.25%) Painless with intravascular injection and painful with extravascular injection Allergy is not rare (including allergic shock, and cardio respiratory arrest) Rare anaphylaxis	FDA approved for treating vascular ectasias of the lower extremity; never formally investigated as a sclerosant agent for varicose and telangiectatic veins Trombovar[®] and Tromboject[®] are licensed by Health Canada for local injection in sclerotherapy
Polidocanol (POL) Brand names: Aethoxysclerol [®] , Aethoxysclerol [®] , Aethoxysclerol [®] , Etioxisclerol [®] , Sotrauerix [®] , Sclerovein [®]	- detergent (emulsifier); mid-potency sclerosing effect; effective at low concentration - commercially available in 0.5% to 5% concentrations; - can be used for any dilated vein (higher concentrations for large veins) - generally used for medium-sized varicose veins and telangiectasias (0.25% to 0.75%)	Lowest risk for pain Moderate risk for skin necrosis Pigmentation at high concentrations Urticaria (immediate) at injection site Ulceration Rare anaphylaxis	Not FDA approved; currently undergoing review for FDA approval Aethoxysclerol[®] is licenced by Health Canada for esophageal varices and needs special approval from Health Canada for leg vein sclerotherapy ²¹
Sodium morrhuate (SM) Brand names: Scleromate [®]	- detergent; biological extract rather than synthetic extract and composition varies from lot to lot; it is unstable in solution - used for varicose veins	Pain Pigmentation Necrosis of skin Highest risk for anaphylaxis	FDA approved for treating vascular ectasias of the lower extremity

Table 2: Sclerosing agents (cont'd)

Agent (brand names)	Description and Usage	Complication profile	Regulatory status
Ethanolamine oleate (EO) Brand names: Ethamolin®	- detergent; viscous and difficult to inject	Pigmentation Necrosis of skin Pain Pulmonary complications Acute renal failure Hemolytic reactions Risk of urticaria and anaphylaxis	FDA approved for esophageal varices
Polyiodine iodine (PII) Brand names: Variglobine® Varigloban® Sclerodine®	- chemical irritant; strong sclerosing effect; dark brown color - is used at concentrations of 0.2% to 12% - results in localized sclerosis - is used for truncal varicose veins and incompetent perforators - can be diluted for use in reticular and telangiectatic veins	Pain on injection Necrosis of skin Renal insufficiency Anaphylaxis Iodine hypersensitivity reactions (contraindicated in the presence of hyperthyroidism and in patients with history of iodine allergy)	Not FDA approved; Sclerodine® licensed by Health Canada for local injection in sclerotherapy
Chromated glycerin Brand names: Chromex® Scleremo®	- chemical irritant; weak sclerosing effect; it is viscous and requires dilution prior injection - produced as a 72% solution - used for telangiectasias	Pain and cramping Very low risk of pigmentation/ulceration Very rare allergic reaction Ineffective sclerosis	Not approved by FDA for use; not available in North America ^{20, 21} Available in Europe ²¹

APPENDIX C: REPORTED RESULTS AND METHODOLOGICAL QUALITY OF REVIEWED RCTS

Table 3: RCTs on the use of sclerotherapy for varicose veins ⁶⁸⁻⁷²

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Labas et al. 2003 ⁶⁸ Age: not mentioned Gender: not mentioned Included: patients with CVI (no details provided) Excluded: not clear	Sample size: 1622 patients Protocol: 454 treated by Sigg's technique using POL (Aethoxysclerol®); 876 treated by Fegan's technique using STD (Fibroven®); and 292 treated by Fegan's technique using STS combined with POL (Fibroven®+ Aethoxysclerol®) Blinding: no blinding Pre- and post-treatment evaluation: all patients underwent the phlebological protocol to localize varices, ulcers, eczemas, pigmentation and perforators; incompetent perforators identified by phlebography, Duplex scan sonography and clinically; in some complicated cases photodocumentation used to safely recognize recurrence; control investigation done by independent group of surgeons Sclerotherapy technique: The techniques of empty vein, bubble air, uninterrupted 6-week compression and forced mobilisation were used in all patients. Success/Failure criteria: results considered "good" in cases of disappearance of varices; reduction of edemas; reduction of eczemas, healed ulcers, and relief of symptoms such as night cramps, pains, fatigue, and heaviness; Outcomes: results reported in terms of "average cure rate" (which was not defined in the published report of this RCT) Follow-up: 6 mo; 5 y;	Results: Sigg's technique (POL): "average cure rate" of 67.47 after 6 mo, and of 60.3% after 5 y; Fegan's technique (STS): "average cure rate" of 83.6% after 6 mo and of 78.54% after 5 y; Fegan's technique (POL+STS): "average cure rate" of 86% after 5 y Statistically significant differences ($p < 0.05$) found only by disappearance of varices and reduction of pain in favor of Fegan's technique. Side effects/Complications: Complications such as local necrosis, hyperpigmentation, and telangiectasis occurred more in patients treated with STS alone ($p < 0.001$). More significant complications such as hypertension and collapse occurred in patients treated with POL ($p < 0.05$)



Table 3: RCTs on the use of sclerotherapy for varicose veins (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
McCoy et al. 1999⁶³ Age: 21 to 76 y (mean 44 y) Gender: all women Included: patients with primary leg idiopathic telangiectasia, with symmetrical areas of vessels on both legs and identifiable reticular feeding veins Excluded: legs with telangiectasia around ankles or clusters of microvessels secondary to surgical scars; previous sclerotherapy, clinical or Duplex evidence of major saphenous or large perforator incompetence, history of ischemic heart disease, vasculitis, diabetes, pregnancy or regular use of anticoagulants	Sample size: 81 patients Protocol: morphologically similar telangiectasia and reticular feeding veins identified in matching locations on legs of each patient, one leg randomly assigned to be injected with 3mL HS 20% (2 mL of 30% saline plus 1 mL of 2% lignocaine hydrochloride), other leg with 1% POL; Blinding: patients and non-treating physician were blinded to sclerosants Pre- and post-treatment evaluation: clinical evaluation by treating physician; photographic evaluation by non-treating physician; treatment sites photographed (prior to treatment and 2 mo after both legs treated) using same camera, lighting conditions, and focal distance, with patient standing. Sclerotherapy technique: supine position; sufficient solution to blanch a reticular system and all visible branches and telangiectasia (not specifically recorded); reticular veins injected first, all approached in a "downstream" direction; one treatment per leg; immediate local compression with cotton balls (tape fixation); no graduated compression after treatment Success/Failure criteria: not clearly stated	Results: All legs: mean patient satisfaction score of 7.11 (SD=1.74), mean clinical assessment score of 7.26 (SD=1.47); mean photo rated score of 7.41 (SD=1.5); NSS difference between photo rated score and clinical assessment score (p=0.2); POL: patient satisfaction score of 7.20 (SD=0.19), mean clinical assessment score of 7.26 (SD=0.21), mean photo rated score of 6.93 (SD=0.20); HS: patient satisfaction score of 7.23 (SD=0.14) (reported as SS greater satisfaction with HS than with POL; p=0.4), mean clinical assessment score of 7.56 (SD=0.14), mean photo rated score of 7.3 (SD=0.19); Side effects/Complications: Pain score for all legs 3.31 (SD=1.60); injections with HS rated as SS more painful than POL (p=0.00001); Five patients returned before 2 mo due to uncomfortable thromboses (in 4 HS-treated legs, and in 1 POL-treated leg); Some evidence of matting in 29 POL-treated legs (31%) and in 25 HS-treated legs (31%); Staining SS more common in POL treated legs (73%) than in HS treated legs (55%) (p=0.003); No ulcers and systemic allergy with either HS or POL One patient reported significant swelling and itching in POL treated leg for several days after treatment.
	Outcomes (measures): pain (score 0 not painful to 10 extremely painful), patient's satisfaction (scale 0 not satisfied to 10 completely satisfied), clinical assessment ((treating physician's evaluation (scale 0 no improvement to 10 complete disappearance) based on estimated percentage of vessel clearance compared to pre-treatment photos)) and blinded assessment of improvement by non treating physician before and after photographs (scale 0 to 10). Adverse effects (telangiectatic matting and hemosiderin staining) scores by treating physician at 2 mo (0 not present to 3 severe) Follow-up: 2 mo	

Table 3: RCTs on the use of sclerotherapy for varicose veins (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Hamel-Desnos et al. 2003⁷² Age: 18-80y Gender: not mentioned Included: incompetence in GVS (pathological reflux in GVS of > 1sec; vein diameter between 4 and 8 mm; patient's age between 18 and 80 ys; signed informed consent) Excluded: mental or psychiatric impairment; chronic liver disease or renal insufficiency; pregnancy or lactation or risk of pregnancy; progressive malignant disease; cardiac or respiratory insufficiency; history of DVT; coagulopathy and a known allergy to POL or one of the ingredients of Aethoxysclerol®	Sample size: 88 patients Protocol: after randomization, 45 patients received sclerotherapy using sclerosing foam and 43 were treated with sclerotherapy using sclerosing liquid; no concomitant treatments were carried out; team consisted of 6 investigators, one statistician and one scientific adviser. Blinding: no blinding Pre- and post-treatment evaluation: Doppler ultrasound examination was performed on day 0 (day of inclusion) and after 3 weeks, 6 mo, 12 mo, 18 mo, and 24 mo Sclerotherapy technique: Administration of 3% POL either in liquid form or foam (identical volumes) performed by direct puncture of GVS into upper third of the thigh (average of 8 to 10 cm from saphenofemoral junction) using US guidance; DSS method used to prepare foam; only one injection of 2.0 or 2.5 mL liquid or foam (depending on diameter of GSV) was allowed; foam injection was given either directly using a 10 mL syringe or with a 2.5 mL syringe after transferring the foam via connector; no concomitant treatments; elastic compression and non-steroidal anti-inflammatory drugs were used only if secondary cutaneous inflammation occurred. Success/Failure criteria: not clearly stated (it appears success is considered in terms of elimination of reflux in GSV) Outcomes (measures): primary evaluation criterion was elimination of pathological reflux in GSV (as assessed by Doppler (Duplex) ultrasonography); the secondary criteria were the length of the parietal reaction (as assessed by Doppler ultrasonography), the time of recanalization and the incidence of side effects. Follow-up: 3 wks, 6 mo, 12 mo, 18 mo, and 24 mo.	Results: SS differences in terms of elimination of reflux in GSV between sclerosing foam (DSS) and sclerosing liquid at 3 weeks ($p < 0.01$): 84% elimination of reflux in GSV DSS after foam (in 38 out of 45 patients) compared to 40% after sclerosing liquid (in 17 out of 43 patients). At 6 mo, 6 recanalizations were found in the group treated with sclerosing liquid vs. 2 recanalizations in the group treated with DSS foam. After 1y, no additional recanalization was observed in either group. Length of parietal reaction was clearly superior with foam: reaction of venous wall was almost twice as long with foam as with liquid (average of 28 cm for foam vs. 15 cm for liquid). Side effects/Complications: Follow-up at 3 weeks: 5 cutaneous inflammations (3 in liquid group and 2 foam group) and 1 hemaloma (in foam group); no venous thrombosis, no allergy, no skin necrosis observed in either group.

Table 3: RCTs on the use of sclerotherapy for varicose veins (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Lupton et al 2002⁷⁰ Age: 27-68 y (mean 45 y) Gender: all women Included: patients with skin phototypes I-III, superficial leg telangiectasia (0.1mm-0.5 mm in diameter, mean 0.5 mm) Excluded: patients with prior lower extremity telangiectasia treatment, clinical evidence of severe vascular incompetence, on anticoagulant treatment, or those currently pregnant or breastfeeding	Sample size: 20 patients Protocol: patients randomized to receive 2 consecutive treatments (at 1 mo interval) with laser irradiation to telangiectases on one leg and with sclerotherapy on the other leg; size matched vessels on thighs, knees, calves, ankles and popliteal fossae were treated by the same operator. Blinding: assessors were blinded Pre- and post-treatment evaluation: not clear whether photographic documentation was obtained before treatment. Post treatment photographic documentation and clinical improvement scores. Sclerotherapy technique: 0.25% STS (Sotradecol®, Ekins-Sinn Inc, Cherry Hill, NJ); sufficient amount injected to blanch vessels and all visible tributaries (range of 2-10ml), graduated compression stockings of 20-30 mmHg applied for 48 hours after treatment Laser irradiation technique: long-pulsed 1064 nm Nd:YAG laser (Varia, CoolTouch Laser Corp, Auburn, LA), of 25 msec duration for smaller vessels, and of 50 msec for veins >0.5mm in diameter; delivered through a 5 mm collimated spot size at 1Hz, cooling with cryogen spray Success/Failure criteria: not clearly described Outcomes (measures): photographic documentation and clinical improvement scores on a scale of 0 to 3 by 2 independent assessors at follow-up visits; side effects recorded at each session and follow-up visit Follow-up: at 1 mo after first session and at 1 and 3 mo after 2nd session	Results: clinical improvement score 26-50% for both sclerotherapy treated legs and for laser treated legs at 1 mo after 1st session at 1 mo after 2nd session, improvement score of 51-75% for sclerotherapy treated legs and 26-50% for laser-treated legs at 3 mo after 2nd session, improvement score of 51-75% for sclerotherapy treated legs and 26-50% for laser treated legs Side effects/Complications: n=14/20 (70%) had mild pain associated with both treatments transient local tissue erythema and edema reported by 95% of patients for sclerotherapy treated legs and by 75% of patients for their laser treated legs transient post-inflammatory hyperpigmentation developed in 2 patients (10%) on their sclerotherapy treated legs (both patients had skin phototype III) no cases of vesiculation, fibrosis or scarring after either treatment

Table 3: RCTs on the use of sclerotherapy for varicose veins (cont'd)

Study and patient characteristics	Study characteristics	Reported results and adverse effects
Belcaro et al. 2000 ⁷¹ Age: between 52±6 and 53±5 y Gender: 51 males and 45 females completed 10-y follow-up Included: age 40-60 y; simple superficial venous incompetence (uncomplicated by phlebitis, hemorrhage or ulcerations); Color duplex documented incompetence of SFJ and other venous sites (including thigh and calf perforators) Excluded: previous DVT, episodes of superficial thrombophlebitis, obesity, diabetes, bone/joint problems, hypertension, other significant cardiovascular problems requiring medication, and other clinically significant diseases; previous treatment with surgery and/or sclerotherapy for venous insufficiency of any limb	Sample size: 150 patients initially randomized, 29 refused treatment or follow-up or failed to undergo planned treatment; analysis and data reported only for those who completed 10 y follow-up (96/121 who received treatment); Protocol: patients randomized to receive endovascular sclerotherapy (Grp A, n=39), surgery and sclerotherapy (Grp B, n=40) or surgery only (Grp C, n=42); no other treatment performed for 10 y; Blinding: no blinding Pre- and post-treatment evaluation: incompetence evaluated with: color Duplex in association with high-resolution US scanner (pre-treatment and at every follow up), AVP (pre-treatment, and at 10 y), strain gauge plethysmograph; Endovascular sclerotherapy (ES): Venocath endovascular catheter (Abott) introduced in GSV under local anesthetic, catheter tip progressed to SFJ and imaged by high resolution US system (ATL Ultramark 9, 7.5 probe) and injected 5-10 ml POL (3%, heated at 45°C); after withdrawal of catheter, the junction region was pressed with cotton balls and Tensoplast (elastic adhesive bandage) for 3 weeks; TED (Kendall, Mansfield, USA) graduated compression stockings applied over elastic bandage; Compression sclerotherapy: provided within 3 mo after ES in Grp A and after surgery in Grp B (for residual veins); the compression therapy used POL (3% for veins > 3 mm; 2% for veins = 2 mm; 1% for veins ≤ 1 mm); compression achieved with cotton swabs and local application of Tensoplast; TED graduated compression stockings applied over elastic bandage; compression therapy applied for 3 weeks for veins > 3 mm and for 1 week for veins = or < 1 mm) Surgery: flush ligation of incompetent SPJ and collateral veins under spinal or general anesthetic; most important reflux sites detected by color Duplex and marked before surgery; no stripping used; Success/Failure criteria: not clearly described Outcomes (measures): incidence of residual incompetence at 1y, 5y and 10 y; cost evaluation Follow-up: after post-surgical evaluation at 10 days, and at 1, 3 and 6 mo, then every 2 y for 10 y	Fifty-four dropouts due to non-medical problems (loss to follow-up, failure to comply with the 10 y no treatment policy); excluded subjects comparable for age and sex distribution to those who completed follow-up. Results: 25 treated patients (21%) did not complete 10 year follow-up (loss to follow up or failure to comply): 7 Grp A, 9 Grp B and 9 Grp C At 10 y no incompetence observed in subjects treated with SPJ ligation (Grp B and Grp C) In Grp A 18.8% of SFJs were patent and incompetent and in 43.8% of limbs the distal venous system was still incompetent as compared to 16.1% in Grp B ($p < 0.05$) and 36% in Grp C ($p < 0.05$ vs Grp B and $p = 0.05$ vs Grp A). Color duplex of GSV indicated atrophy or obstruction of a segment (mean 6.7 cm) after SFJ ligation (mean 4.2 cm after ES). Mean cost (for evaluation and treatment) of ES was 68% of cost for surgery alone (considered standard cost for this indication) Mean cost of surgery and sclerotherapy was 122% of standard cost (for surgery alone). Side effects/Complications: No DVT or superficial vein thrombosis observed following surgery or at 10 y follow up.

Table 4: A quality assessment of the reviewed RCTs ⁶⁸⁻⁷²

Reviewed RCT	Randomization process	Blinding	Comments
Labas et al. ⁶⁸	- randomization method not stated - allocation concealment not stated	no blinding performed	- no description of sample size calculation (not clear whether study included all patients treated between 1991 and 2000) - source of study population not described; - inclusion/exclusion criteria not identified; no description of patients provided - distribution of known confounders not described - setting not stated; no information on sclerotherapy providers' expertise and training - not clear whether independent evaluators were used only for photographic assessment or not - outcome measures not clearly mentioned and described - not clear who examined the adverse effects - data not clearly and adequately reported; average cure rate not defined
McCoy et al. ⁶⁹	- randomization method not stated - allocation concealment not stated - each patient acted as her own control	- patients blinded to sclerosants - non-treating physician (evaluator of photographs) blinded to sclerosants	- no description of sample size calculation - source of study population not clearly described - distribution of known confounders not described - setting not stated; no information on sclerotherapy providers' expertise and training - independent evaluators only for photographic assessment - adverse effects examined by treating physician
Hamel-Desnos ⁷²	- randomization method not stated - allocation concealment not stated	no blinding performed	- source of study population not described - no description of patients provided - distribution of known confounders not described - setting not stated; no information on sclerotherapy providers' expertise and training - not clear who performed outcome evaluation (treating physicians or external observers) - not clear who examine the adverse effects

Table 4: A quality assessment of the reviewed RCT (cont'd)

Reviewed RCT	Randomization process	Blinding	Comments
Lupton et al. ⁷⁰	- randomization method not stated - allocation concealment not stated - each patient acted as her own control	2 independent assessors (using photographic documentation and clinical scores) blinded	- no description of sample size calculation - source of study population not clearly identified - distribution of known confounders not described - setting not stated, no information on sclerotherapy providers' expertise and training - outcome measures not adequately described - not clear who examined the adverse effects - data not clearly and adequately reported
Belcaro et al. ⁷¹	- randomization method not stated - allocation concealment not stated	no blinding performed	- no description of sample size calculation - source of study population not clearly identified - setting not stated, no information on sclerotherapy providers' expertise and training - not clear who performed outcome evaluation, treating physician(s) or external observers - data reported only for those who completed the follow-up

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